Claim 4, line 1, please cancel "effected" and insert - -performed- -.

REMARKS

Applicants have amended the claims in order to place the application in condition for allowance. If this amendment does not place the application in condition for allowance, the undersigned attorney would like to conduct an interview with the Examiner in an effort to place the application in condition for allowance.

The claims have been amended to more particularly define the invention taking into consideration the outstanding Official Action. Claim 1 has been amended to correct an obvious typographical error in the spelling of cobalamin and it is most respectfully requested that the objection to the claims because of this be withdrawn.

Applicants have carefully considered the rejection of claims 4 under the second paragraph of 35 USC §112 and request that this rejection be withdrawn. The claim language has been amended to state that an automated process is performed. The meaning of this claim is definite to one of ordinary skill in the art to which the invention pertains. It would be apparent to one of ordinary skill in the art that the advantage of the current invention is that the cobalamin is separated and concentrated in a form suitable for automated determination of cobalamin. The cobalamin could be determined by any suitable automated means known to those skilled in the art. Therefore, claim 4 is clear in its meaning. It is noted that claim 4 has not been rejected under the first paragraph of 35 USC §112.

At the outset, Applicants wish to note that not all transcobalamin II in a sample will be bound to, cobalamin. Only 6 to 25% of TC II is bound to cobalamin, as demonstrated in the attached figure. It will be noted that the majority of cobalamin binds to Haptocorrin. See also page two of Applicants' specification, third and fourth paragraphs. Using the presently claimed assay of the invention, a separation and concentration of biologically functional cobalamin is performed, which leads to an accurate indicator of cobalamin levels and hence deficiency. The presently claimed invention is not obvious from the prior art.

The rejection of claims 1, 5-7, 10, 12, 16-20, 26, 42-44, 47-48 and 50 under 35 USC § 103(a) as being obvious over McLean et al (Blood, vol 89) in view of Houts (US 4465775) has been carefully considered but is most respectfully traversed. Claim 1 as currently pending relates to the use of specific binding ligands for transcobalamin II in order to separate and concentrate the Holo transcobalamin II, from which the cobalamin is released and determined. Thus, the method of the invention provides an improvement over the prior art in that the cobalamin to be determined is separated and concentrated prior to an assessment of quantity. The inventors have discovered that the measurement of cobalamin bound to transcobalamin II is an effective indicator of the level of cobalamin in a sample, using the method as described in claim 1 of the application. Claim 1 contains specific claim limitations, contrary to the statement in item 13 of the Official Action, which is specifically traversed. These claim limitation cannot be ignored. Moreover, no one previously has been able to produce a reliable, direct quantification of Holo-TC II levels in a sample.

McLean et al relates to a proliferation assay using antibodies which bind to transcobalamin II to determine whether such antibodies may be used for cancer therapy. There is no indication in this paper that the level of cobalamin in a sample could be quantitated by means of capturing transcobalamin II. In fact, this paper points towards the presence of other cobalamin binding proteins (see page 235, first paragraph). Thus, the authors in no way indicate that transcobalamin II could be utilized in an assay to determine whether a subject has a cobalamin deficiency. Further, the Examiner has specifically pointed towards the ELISA assay of McLean in rejecting the above-mentioned claims. It should be mentioned here that such an ELISA assay was performed to analyze whether the monoclonal antibodies bound to transcobalamin II.

In ELISA, two antibodies are required to capture and detect the antigen, and such a method is laborious, involving multiple incubation and washing steps. In this type of assay, the antigen remains bound to the capturing assay, and it is necessary to use two antibodies which bind to different epitopes on the antigen. In the presently claimed method, specific binding ligands (not limited to antibodies) are used to separate and concentrate the transcobalamin II. The cobalamin bound to the antigen (holo-TC II) is

released from the specific binding ligand, which plays no further role. In short, McLean makes no suggestion that the antibodies would be suitable for concentrating cobalamin in a sample, as claimed in claim 1 of the current application.

Applicants wish to direct the Examiner's attention to the basic requirements of a prima facie case of obviousness as set forth in the MPEP. Section 2143 of the MPEP states that to establish a prima facie case of obviousness, three basic criteria first must be met. First, there must be **some suggestion or motivation**, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest **all the claim limitations**.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicants most respectfully submit that the obviousness rejections in the Official Action do not meet the MPEP standards.

Turning now to Houts (4,465,775), Applicants most respectfully submit that this positively teaches away from the presently claimed method. In this patent, the applicant teaches the use of proteins that bind to cobalamin (vitamin B12) for assaying cobalamin. Applicants wish to point out to the Examiner that in the method of the present invention, specific binding ligands for TC II are used, **not specific ligands for cobalamin**. In the assay of the present invention, the cobalamin is indirectly separated from the serum sample by virtue of its binding to TC II. In the assay of Houts, cobalamin would have to be in a free state (i.e. not bound to a binding protein) in order to be able

to bind to a binding protein. Further, Houts states that the most effective binding protein to use in their assay is intrinsic factor (page 1, line 64), teaching away from TC II. Therefore, one of ordinary skill in the art to which the invention pertains would be in no way motivated by the disclosure in Houts, to separate TC II from serum to measure cobalamin. In fact, he would be lead to testing for cobalamin that was present in a free state (i.e. not bound to any protein), as such binding proteins are used in the assay).

Therefore, contrary to the assertions in the Official Action, Houts does not teach a method of assaying TC II. It teaches a method of assaying cobalamin. For the avoidance of doubt, TC II and cobalamin are entirely different entities. Cobalamin is vitamin B12 and binds to TC II. It appears that this issue may be confused in the Official Action, see page 5 wherein it is stated that "Houts teaches a method of assaying TC II or any cobalamin analogue". This is not true and this statement is specifically traversed. The assay of the present invention essentially measures only the cobalamin that is bound to TC II, and the method of claim 1 allows for the separation and concentration of the cobalamin bound to TC II to enable cobalamin quantification. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 9, 11, 24-25 and 35-36 as obvious over McLean et al (Blood, vol 89) in view of Houts (US 4465775) and in further view of Herbert (US. 4680273) under 35 USC §103, has been carefully considered but is most respectfully traversed. As previously discussed, the McLean et al and Houts references do not render the clams upon which claims 9, 24-25 and 35-36 are dependent obvious. Herbert does not overcome the deficiencies of the primary references thus rendering the rejections to these claims moot. However, for the avoidance of doubt, Herbert does not teach separation and concentration of cobalamin via binding of TC II to a specific binding ligand. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The Examiner has further combined the citations of McLean and Houts with Allen (US 5,374,560), and in light of this combination, rejected claims 4 and 49. Again, the citations of McLean and Houts have been dealt with previously, and therefore the points raised by the Examiner are moot. Allen deals with a method for detecting folic acid or

cobalamin deficiency which involves the assessment of cysathionine content in body fluid. Thus, this teaches away from the use of TC II in the assay of cobalamin, automated or not. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of Claims 27 to 33 as obvious in light of McLean, Houts and Hoyle (US 5,451,508) has been carefully considered but is most respectfully traversed. As all claims have been shown to be non-obvious over McLean and Houts, this rejection is moot. Hoyle uses antibodies to cobalamin (not transcobalamin II), and therefore does not measure cobalamin bound to TC II. Further, the affinity constants referred to in this citation relate to the binding of cobalamin, not transcobalamin, and therefore have no relevance to the presently claimed invention. Accordingly, it is most respectfully requested that this rejection be withdrawn.

Applicants submit herewith the necessary certified copy of the priority document to complete the claim for priority. An acknowledgment of the claim for priority in the next Official Action is most respectfully requested.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

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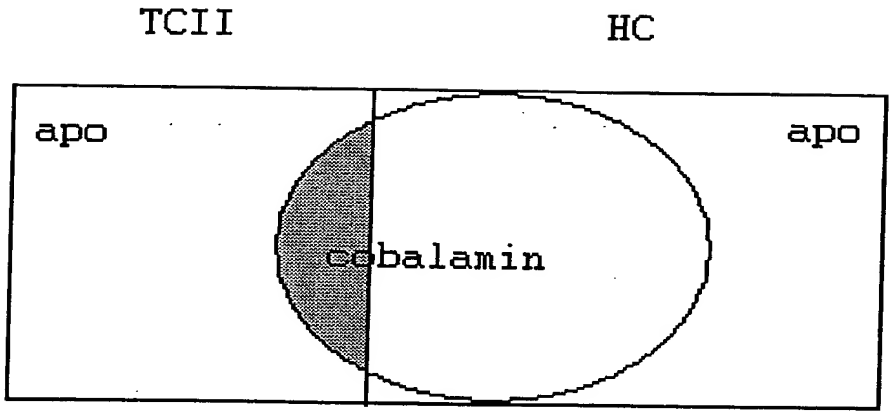
FIGURE 1



biologically functional cobalamin

TCII Transcobalamin II

HC Haptocorrin